Decision Memo for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N)

Decision Summary

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS will not expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

Back to Top

Decision Memo

TO:

Administrative File: CAG-00144N
Screening DNA Stool Test for Colorectal Cancer

From:

Steve E. Phurrough, MD, MPA
Director, Coverage and Analysis Group

Marcel E. Salive, MD, MPH
Director, Division of Medical and Surgical Services

William Larson, MA
Lead Analyst

Joseph Chin, MD, MS
Medical Officer

Subject: Coverage Decision Memorandum for Screening DNA Stool Test for Colorectal Cancer
Date: April 28, 2008

I. Decision

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS will not expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

II. Background

For many years, screening for colorectal cancer (CRC) with fecal occult blood tests (FOBTs) has been recommended by various professional organizations including the U.S. Preventive Services Task Force (USPSTF available at http://www.ahrq.gov/clinic/uspstf/uspscolo.htm). Specifically, the USPSTF noted “good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer” (USPSTF, 2002). Medicare currently covers 2 stool hemoccult based tests: the guaiac test and the immunochemical test. The advantages of these tests over other CRC screening tests include the relative simplicity, non-invasive nature, wide availability and cost-effectiveness. The main disadvantage is the variable sensitivity of a single stool hemoccult test, estimated at 40% for a guaiac test (USPSTF, 2002).

Recently, mutant (abnormal) (deoxyribonucleic acid (DNA)) in the stool has been targeted as another modality for CRC screening. One such test, PreGen-Plus™ Version 1.1 by Exact Sciences, has been on the market for several years. PreGen-Plus™ Version 1.1 consists of a panel of 23 individual tests to detect 21 specific mutations in the APC, K-ras and p53 genes, a marker for microsatellite instability known as Bat-26, and a marker known as DNA Integrity Assay (DIA®, Exact Sciences 2004 available at http://www.mi3.com/pressreleases/2004.12.22.Exact.pdf). In August 2007, CMS accepted a formal request from Exact Sciences for Medicare coverage of stool DNA testing for CRC screening in average risk individuals. The requestor asks CMS to cover their test every 5 years as an alternative to a screening colonoscopy that may be covered every 10 years or as an alternative to a screening flexible sigmoidoscopy that may be covered every 4 years for such individuals as provided in 42 CFR 410.37(e) and (g). See, also § 1834(d) of the Act.

III. History of Medicare Coverage

The Balanced Budget Act of 1997, Public Law No. 105-33, § 4194 (1997), established coverage for screening colorectal cancer procedures under Medicare Part B, effective January 1, 1998. Medicare currently covers (1) annual FOBTs, (2) flexible sigmoidoscopy every 4 years, (3) screening colonoscopy for persons at average risk for colorectal cancer every 10 years[1], or for persons at high risk for colorectal cancer every 2 years[2], (4) barium enema every 4 years as an alternative to flexible sigmoidoscopy or colonoscopy, and (5) other procedures the Secretary finds appropriate based on consultation with appropriate organizations. Coverage of these screening exams was implemented in regulations through a final rule that was published on October 31, 1997 (Federal Register Notice 10/31/1997, Vol. 62, No. 21, 59079-59082, 59100-59101), and was effective January 1, 1998.

In the Physician Fee Schedule Final Rule for 2003, CMS amended the FOBT screening test regulation definition in CFR 410.37 (a) (2) to provide that it could include coverage of either (1) a guaiac-based FOBT, or (2) other tests as determined by the Secretary through a national coverage determination (Federal Register Notice 12/31/2002, Vol. 67. No.251, 79966, 80040). On November 4, 2003, CMS issued a final Decision Memorandum indicating that effective with that date Medicare would cover a screening immunoassay FOBT on an annual basis as an alternative to the guaiac-based FOBT.

In the Physician Fee Schedule Final Rule for 2003, CMS also amended the colorectal cancer screening test regulation in 42 CFR 410.37 (a) (1) (v) to provide that in addition to the screening test options already covered under the regulation, it could include coverage of additional colorectal cancer screening tests through issuance of a national coverage determination (Federal Register Notice 12/31/2002, Vol. 67, No. 251, 79966, 80040).

Tests performed as a CRC screening test are also frequently used as a diagnostic test. This NCD does not address the use of stool DNA testing as a diagnostic test.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category under part A or part B as a prerequisite to Medicare coverage under the fee-for-service program. Congress has specifically authorized coverage of certain screening tests under part B of the Medicare program and has consistently made necessary conforming changes in order to ensure that payments are made. Colorectal Cancer Screening Tests have a benefit category under §1832, §1861(s)(2)(R) and §1861(pp) of the Act. Specifically, CMS is using the national coverage determination authority under section 1861(pp)(1)(D) and 42 CFR 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include coverage of the DNA stool test.

IV. Timeline of Recent Activities

August 1, 2007	Request for consideration of EXACT Sciences' PreGen-Plus™ screening DNA stool test produce accepted by Coverage and Analysis Group.
September 1, 2007	Initial 30-day public comment period closes.
November 15, 2007	CMS sends letter to EXACT Sciences inquiring about the marketability of their test, in light of FDA's Warning Letter of October 11, 2007, indicating serious regulatory problems with their test (Appendix A).
	CMS meets with EXACT Sciences to discuss the FDA's Warning Letter, including when the FDA's concerns might be resolved and their impact on CMS' NCD process.
December 14, 2007	
	CMS receives letter from EXACT Sciences requesting that they be allowed to withdraw their test from the NCD evaluation process pending the resolution of the FDA's regulatory concerns.
December 20, 2007	
	CMS posts a technology assessment, including a cost effectiveness analysis for use of this test as a screening test, which was requested from the Agency for Healthcare Research and Quality.
January 9, 2008	
	Proposed decision memorandum posted; 30-day comment period begins.

V. FDA Status

The FDA would consider a test for DNA detection in stool intended to replace fecal occult blood detection to be a class II device (moderate risk), which would require a Premarket Notification (510(k)) to the FDA prior to marketing. Such a test intended to replace colonoscopy would represent a device with a new intended use and would be considered a class III device (high risk) by the FDA. Class III devices require premarket approval by the FDA prior to marketing.

On October 11, 2007 EXACT Sciences received a warning letter from the FDA that stated that the PreGen-Plus™ test is a medical device that requires FDA clearance or approval prior to marketing and is currently being marketed in violation of the Federal and Food Drug and Cosmetic Act (Appendix A). To date, EXACT Science's PreGen-Plus™ test has not been cleared or approved by FDA.

VI. Evidence

A. Introduction

In general, for a test to be considered a good screening test, a number of factors must be evaluated, including the sensitivity, specificity, simplicity, cost, safety, availability and acceptability. CMS reviewed the definitions of these characteristics and their application to colorectal cancer screening in 2003 in the context of the national coverage determination on screening immunoassay fecal occult blood test (Available at http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87). Given the existing CRC screening options, experts recommend choosing a specific strategy for a given patient based upon patient preferences, medical contraindications, patient adherence and available resources for testing and follow-up (USPSTF 2002).

In addition to performance characteristics, morbidity and mortality have been studied as outcomes of colorectal cancer screening. For example, FOBT screening has been shown to improve mortality (USPSTF 2002). Since a number of screening tests are available and covered for colorectal cancer, how a new test should be used and how it fits into the current recommendations for screening also should be considered.

Specifically for stool DNA testing, this determination focused on the only test (PreGen-Plus™ Version 1.1) that was commercially available when we initiated the analysis. PreGen-Plus™ Version 1.1 was also the test panel that was used in the published studies. PreGen-Plus™ Version 2.0 is reportedly in development but is not considered in this decision.

Literature Search

CMS searched PubMed from 2000 to present. General keywords included stool/fecal DNA and colorectal cancer. Publications that presented original data on screening with DNA testing were considered. Abstracts, animal studies and non-English publications were excluded.

B. Discussion of evidence reviewed

1. External technology assessments

Zauber AG, Lansdorp-Vogelaar I, Wilschut J, et al. Cost-effectiveness of DNA stool testing to screen for colorectal cancer. AHRQ Technology Assessment Program 2007
This can be found (http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=212) .

In 2007, Zauber and colleagues reported the results of an analysis "to assess the cost-effectiveness of screening for CRC with the DNA stool test in comparison to the currently recommended CRC screening strategies." The cost-effectiveness analysis was based upon simulations using 2 well accepted, validated models: the MISCAN-Colon (Microsimulation model of the Memorial Sloan-Kettering Cancer Center and ErasmusMC) and SimCRC (Microsimulation model of the University of Minnesota and Massachusetts General Hospital). The models incorporate literature-derived estimates of sensitivity and specificity of the DNA stool test for detecting adenomas by size and for CRC. They also incorporate direct medical costs estimated using current CMS reimbursement rates, an estimate for the cost of the DNA stool test, and derived beneficiary costs. The analysis used a modified societal perspective and included sensitivity and threshold analyses. The authors concluded: "These results suggest that screening for CRC with the DNA stool test version 1.1 does provide a benefit in terms of life-years gained compared with no screening but the cost, relative to the benefit derived and to the availability and costs of other CRC screening tests, would need to be in the range of $34-$60 to be a non-dominated option. Only if significant improvements for the DNA stool test characteristics or relative adherence with DNA stool testing compared with other available options can be demonstrated, will stool DNA testing at the current costs of $350 be cost-effective. These estimates are based on a third-party payer analysis on an unscreened 65-year old cohort. Threshold costs are similar for a 50-year old cohort, but can be somewhat higher from a modified societal perspective ($88 to $134 for 5-yearly testing and $73 to $116 for 3-yearly testing)."

Blue Cross Blue Shield Technology Evaluation Center. Fecal DNA special report: Analysis for colon cancer screening. BCBS TEC Assessment Program 2006; Volume 21, No. 6 (at http://www.bcbs.com/blueresources/tec/vols/21/21_06.pdf).

In 2006, the Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC) published an assessment to "provide information relevant to the evaluation of fecal DNA screening for colon cancer in asymptomatic patients at average risk." The special report addressed: "the current context of existing and emerging screening tests for colorectal cancer, including current published recommendations; the molecular basis for fecal DNA screening and the commercially available fecal DNA screening test, PreGen-Plus™; direct and indirect evidence comparing the performance of PreGen-Plus™ testing to other methods of colon cancer screening; evidence regarding the likelihood of compliance with fecal DNA screening; and available cost-effectiveness analyses of fecal DNA screening." One study (Imperiale 2004) was evaluated for clinical utility of fecal DNA screening. The TEC concluded: "Fecal DNA testing is a noninvasive colorectal cancer screening technology that may eventually offer sensitivity for cancer closer to that of colonoscopy than that of conventional, guaiac-based FOBTs. Although the impact of fecal DNA screening on cancer morbidity and mortality has not yet been studied, it seems reasonable to assume that attaining sensitivities equal to or better than that of FOBT would result in similar or improved outcomes. However, several questions remain before fecal DNA screening can be widely recommended:

- Can sensitivity for large adenoma be significantly increased compared to FOBT?
- Can false-positive rates be maintained appropriately low for a screening program?
- What is the final configuration of the PreGen-Plus™ test and what are its published performance characteristics in an average-risk screening population?
- What is the optimal screening interval?
- Which patients should not be screened with fecal DNA testing?
- Does the test improve compliance with colorectal cancer screening?

- Is the test cost-effective?"

2. Internal technology assessment

Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroentereology 2000;119:1219-1227.

In 2000, Ahlquist and colleagues reported the results of a retrospective case series of 61 patients to explore "the feasibility of a stool assay panel of selected DNA alterations in discriminating subjects with colorectal neoplasia from those without." Stool specimens were "selected from a freezer archive to yield subject groups with verified colorectal adenocarcinoma, colorectal adenomas $\geq$ 1.0 cm, and colonoscopically normal colons." Stool specimens were "collected within days before cathartic preparation for a scheduled colonoscopy, which served as the criterion standard." Specimens were frozen at -80°C. Specimens were then sent to Exact Sciences and tested for 15 point mutations on the K-ras, APC, and p53 genes, Bat-26 marker of microsatellite instability.

Of the 61 patients, 22 had colorectal cancer, 11 had adenomas and 28 were normal on colonoscopy. The authors reported: "Analyzable human DNA was recovered from all stools. Sensitivity was 91% (95% confidence interval, 71%-99%) for cancer and 82% (48%-98%) for adenomas >1 cm with a specificity of 93% (76%-99%). Excluding K-ras from the panel, sensitivities for cancer were unchanged but decreased slightly for adenomas to 73% (39%-94%), while specificity increased to 100% (88%-100%)." They concluded: "Assay of altered DNA holds promise as a stool screening approach for colorectal neoplasia. Larger clinical investigations are indicated."

Tagore KS, Lawson MJ, Yucaitis JA, et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. Clinical Colorectal Cancer 2003;3:47-43.

In 2003, Tagore and colleagues reported the results of a case series of 292 patients to "provide an estimate of the sensitivity and specificity of a multitarget assay panel (MTAP) of stool DNA changes." Stool specimens were obtained before colonoscopy from 80 patients with colorectal neoplasia and 212 with normal colonoscopy results or small polyps only. Stool specimens were frozen, sent to Exact Sciences for DNA analysis, and tested for 21 mutations in the K-ras, APC and p53 genes, BAT-26 marker and a marker of disordered apoptosis (DIA®).

Of the 80 patients, 52 had invasive colorectal cancer and 28 had advanced adenomas. The authors reported that the MTAP "detected 33 of 52 patients (63.5%, 95% confidence interval [CI], 49.0%-76.4%) with invasive colorectal cancer" and 16 of 28 patients with advanced adenomas (57.1%). Of the controls, the MTAP was "positive in 8 of 212 subjects for whom colonoscopy was either completely negative or revealed only small polyps, yielding a specificity of 96.2% (95% CI, 92.7%-98.4%)." The authors concluded: "The MTAP identified 49 of 80 patients with advanced colorectal neoplasia (61.2%; 95% CI, 49.7%-71.9%), including patients with invasive cancer (33 of 52; 63.5%) and advanced adenomas (16 of 28; 57.1%). Compared with historic FOBT results for single-point-in-time studies, the detection of DNA abnormalities in stool appears to be substantially more sensitive, with comparable specificity. Importantly, the sensitivity for early stage lesions (AJCC stages 0, I, and II) and other advanced adenomas appears to be similar to that for late-stage lesions (AJCC stage III/IV), suggesting that this modality might be more effective in detecting the lesions that are most curable. The MTAP as a noninvasive screening option may be useful in bringing a larger segment of the population into screening and help screen those patients who can benefit most from colonoscopy."

Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. New England Journal of Medicine 2004;351:2704-14.

In 2004, Imperiale and colleagues reported the results of a cross sectional study of 2507 individuals to compare “an approach that identifies abnormal DNA in stool samples with the Hemoccult II fecal occult-blood test in average-risk, asymptomatic persons 50 years of age or older.” There were no other inclusion criteria listed. Exclusion criteria included prior gastrointestinal bleeding, colorectal cancer, polyps and colonoscopy within 10 years. The fecal DNA test by Exact Sciences (PreGen-Plus™) was used. Colonoscopy was the reference standard test for cancers and polyps. Of the 5486 individuals enrolled, 4404 completed stool tests and colonoscopy. Of these, 2507 were included in the analysis (23 patients with advanced adenomas were excluded, as well as 1874 randomly selected patients with minor polyps or no polyps). For the 2507 patients analyzed, mean age was 69.5 years. Men comprised 44.5% of the analyzed group.

The authors reported the following results: “The fecal DNA panel detected 16 of 31 invasive cancers, whereas Hemoccult II identified 4 of 31 (51.6 percent vs. 12.9 percent, P=0.003). The DNA panel detected 29 of 71 invasive cancers plus adenomas with high-grade dysplasia, whereas Hemoccult II identified 10 of 71 (40.8 percent vs. 14.1 percent, P<0.001). Among 418 subjects with advanced neoplasia (defined as a tubular adenoma at least 1 cm in diameter, a polyp with a villous histological appearance, a polyp with high-grade dysplasia, or cancer), the DNA panel was positive in 76 (18.2 percent), whereas Hemoccult II was positive in 45 (10.8 percent). Specificity in subjects with negative findings on colonoscopy was 94.4 percent for the fecal DNA panel and 95.2 percent for Hemoccult II.”

They concluded: “Although the majority of neoplastic lesions identified by colonoscopy were not detected by either noninvasive test, the multitarget analysis of fecal DNA detected a greater proportion of important colorectal neoplasia than did Hemoccult II without compromising specificity.” In this report, it was unclear why a sample of patients was selected for analysis.

Syngal S, Stoffel E, Chung D, et al. Detection of stool DNA mutations before and after treatment of colorectal neoplasia. Cancer 2006;106:277-283.

In 2005, Syngal and colleagues reported the results of a case series of 91 patients to “1) define the sensitivity of a refined multitarget assay panel (MTAP) for detecting DNA abnormalities in stool specimens collected from a large cohort of individuals with colorectal carcinoma or advanced adenomas; and 2) to prospectively examine whether the mutations detected in stool DNA before treatment persist after surgical resection and/or adjuvant therapy.” Patients with “newly diagnosed colorectal carcinoma or advanced adenoma measuring ≥ 1 cm” were eligible. Stool specimens were collected at least 14 days after endoscopy but before surgery and/or chemoradiation. Specimens were transported from the patients’ home to Exact Sciences directly. The DNA assay consisted of 23 markers [21 mutations in the K-ras, APC, p53 genes, BAT-26 marker and a marker of disordered apoptosis (DIA®)].

A total of 135 patients were enrolled but 8 patients were nonevaluable and 36 provided inadequate specimens. The authors reported: “Overall, 49 of 91 individuals (54%) tested positive with the MTAP test. The sensitivity of the MTAP test was 63% for invasive tumors compared with 26% for AA (advanced adenomas). Individuals whose lesions had a more advanced TNM stage or were located distal to the splenic flexure were significantly more likely to have a positive MTAP test. Of the 79 samples collected at 1–3 months after surgical resection of the neoplasm, 14 (18%) had a positive MTAP result, 12 of which were positive for DIA only. Of those collected at 6–9 months of follow-up, 5 of 72 (7%) tested positive on the MTAP panel.” They concluded: “Although many samples collected 1–3 months after surgical resection of the colorectal neoplasm tested positive on the MTAP, most were negative by 6–9 months, indicating that stool DNA abnormalities disappear after treatment of the neoplastic lesions. Surgery and chemoradiation appear to induce transient DIA abnormalities that may be independent of the presence of neoplasia.”

3. MEDCAC

No MEDCAC was held for this topic.

4. Evidence-based guidelines

We have reviewed the USPSTF recommendations on screening for colorectal cancer in average risk populations and they are silent on the use of the DNA stool test for that purpose.

5. Professional Society Position Statements

An expert panel convened by the American Gastroenterological Association examined stool DNA screening in 2003 and commented that “this approach is promising.” However, they noted that the effectiveness data were not well enough established to be recommended (Winawer et al, 2003).

As indicated in its 2006 “ASGE Guide: Colorectal Screening and Surveillance,” the American Society for Gastrointestinal Endoscopy states that: “Studies evaluating virtual colonoscopy and fecal DNA testing for CRC screening have yielded conflicting results and therefore cannot be recommended.”

Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Published online at: http://caonline.amcancersoc.org/cgi/content/full/CA.2007.0018v1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&titleabstract=guidelines&searchid=1074190906250_391&stored_search=&FIRSTINDEX=0&journalcode=canjclin

The American Cancer Society (ACS), the US Multi-Society Task Force on Colorectal Cancer (USMSTF), and the American College of Radiology published a joint guideline for colorectal cancer screening in 2008. For stool DNA testing, they wrote the following quoted excerpts:

sDNA—Efficacy and Test Performance. Several studies on the sensitivity and specificity of sDNA testing for CRC detection have been published utilizing a panel of DNA markers. Test sensitivity for CRC in these studies ranged from 52% to 91%, with specificity ranging from 93% to 97%. Lower sensitivity in some of these studies has been attributed to suboptimal sensitivity performance of DIA resulting from DNA degradation during transit of specimens to the laboratory. The changes associated with version 1.1 are reported to address these problems. One study utilizing version 1.1 has been published by Whitney et al reporting a sensitivity for CRC of 70%.

sDNA has been compared to a low-sensitivity gFOBT in one large, prospective study of an average-risk screening cohort. Imperiale et al conducted an investigation in a cohort of 2,507 average-risk individuals undergoing colorectal neoplasia screening by 3 modalities: sDNA using the prototype assay (version 1.0), gFOBT (nonrehydrated Hemoccult II), and colonoscopy. sDNA testing had statistically significantly better sensitivity for CRC compared with Hemoccult II (52% versus 13%) and for all cancers and high-grade dysplasia (40.8% versus 14.1%), with comparable specificity. In this study, sDNA was much less sensitive in the detection of all advanced adenomas (15.1%), defined as a tubular adenoma at least 1 cm in diameter, an adenoma with a villous histologic appearance, or an adenoma with high-grade dysplasia, although it still showed superior performance to the comparison gFOBT (10.7%). Data on program performance of sDNA screening are lacking. Information on the sensitivity and specificity of CRC and adenoma detection comes from an evaluation of results from a single test. Also, the currently available sDNA gene test—version 1.1—has not been rigorously tested in screening cohorts but based on available data can be reasonably assumed to perform as well or better than version 1.0. New version assays with better DNA stabilization and simplified genetic analyses may be more sensitive than version 1.0 but require testing in screening cohorts.

sDNA—Benefits, Limitations, and Harms. The primary benefit of sDNA is that this methodology has acceptable sensitivity for CRC and is built upon the concept of detecting molecular markers associated with advanced colorectal neoplasia. It is not dependent on the detection of occult bleeding, which is intermittent and nonspecific, and it requires only a single stool collection. Further, newer versions may have better sensitivity as more is learned about markers that are common across all prevalent CRC, as well as advanced adenomas. sDNA sampling also is noninvasive and lacks physical harm. Patient and provider acceptance of this technique appears to be high, with available data indicating that sDNA is preferred over other tests by some individuals, and among others testing with sDNA, it is at least as acceptable to patients as testing with gFOBT. Berger et al reported that most individuals undergoing sDNA who completed a mailed survey reported satisfaction with the sDNA testing process, and most reported that they would repeat testing if recommended by their physician.

A clear limitation of sDNA testing for the detection of CRC and large adenomas is that test sensitivity is based on a panel of markers that appears to identify the majority of but not all CRC. Further, it is not known what proportion of advanced adenomas is identified with the current commercial version (version 1.1) of the sDNA test. Other potential limitations that have considerable implications for cost-effectiveness are the unit cost of the current test, which is much higher than the other stool tests, and the frequency with which the test should be performed, which is uncertain. Currently, the test is under review by the Food and Drug Administration for 510K certification but is commercially available under the "home brew" category.

An additional issue is the clinical relevance of a positive genetic test without identification of the cause of the abnormality; this has not been studied systematically. At issue for a test that is based on molecular markers is the degree to which a positive test, with no evidence of advanced lesions upon completion of colonoscopy, is truly negative or positive for a lesion that is not yet clinically evident. Osborn and Ahlquist have highlighted the fact that inasmuch as cancers exfoliate cells and that these cells can survive the digestive process and ultimately be excreted in stool, high prevalence supracolonic aerodigestive cancers may also be detected by sDNA. However, at this time, the significance of a positive test result in a patient with a negative follow-up evaluation is unknown.

Quality Assurance. Individuals should be informed about the benefits and limitations of screening for CRC with sDNA, including the facts that at present the test is more sensitive for cancer than advanced adenomas, that the current panel of markers will not identify all cancers, and that a positive test will need to be followed up with colonoscopy. Individuals should also know that the rescreening interval after a negative test is uncertain. Individuals should be made aware that their stool specimen must be packaged and shipped in a customized collection kit that includes a specially designed ice pack. Patients must have access to a working freezer and allow this ice pack to freeze for at least 8 hours prior to use. If the specimen is returned without the ice pack or if there are unforeseen delays in specimen return or processing, the specimen may be rejected….

sDNA—Conclusions and Recommendations. In previous assessments of the performance of sDNA, both the ACS and the USMSTF concluded that data were insufficient to recommend screening with sDNA for average-risk individuals. Based on the accumulation of evidence since the last update of these guidelines, the panel concluded that there now are sufficient data to include sDNA as an acceptable option for CRC screening. As noted above, testing stool for molecular markers is an evolving technology. New iterations of these tests, either technological enhancements of existing tests or completely new test variants, should be carefully evaluated in order to determine that they meet the criteria of detecting a majority of cancers at the time of screening but also have acceptable performance in a screening cohort. While the manufacturer of the one test that is commercially available currently is recommending a 5-year interval for routine screening between examinations with normal results, the panel concluded that there were insufficient data upon which to endorse this interval. Such an interval was judged by the committee to be appropriate only for a test that has very high sensitivity for both cancer and adenomatous polyps—a standard that has not been documented for sDNA to date. At this time, further research is needed to determine the interval between negative sDNA exams. Based on current evidence, the appropriate interval is uncertain.

6. Public Comments

During the initial 30-day comment period, CMS received 154 comments. A complete summary of those comments can be found in our proposed decision memorandum on our coverage website. CMS proposed on January 30, 2008, “not to expand the colorectal cancer screening benefit to include coverage of the screening DNA stool test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review.”

Of the total 154 comments, 146 commenters were in favor of expanding the current colorectal cancer screening benefit to include coverage of the stool DNA screening test. Seven commenters were opposed to the expansion of the colorectal cancer screening benefit to include coverage of the test. One commenter did not express a preference relative to coverage because it indicated that it would be premature to do that because it was currently updating its colorectal cancer screening guidelines and soon would be issuing them.

Public Comments on the Proposed Decision Memorandum

CMS received 9 comments during the final 30-day comment period following publication of the proposed decision. Of the total 9 comments, 5 commenters were in favor of the proposed decision not to expand the colorectal cancer screening benefit to include coverage of the stool DNA screening test and 4 commenters were opposed to the proposed decision.

Professional Societies and Organizations

Comment: The American Cancer Society Cancer Action Network (ACS CAN) indicated that it was in the process of finalizing their colorectal cancer screening guidelines and expected to release them in March of this year. The commenter added that "With respect to the CMS coverage decision, we understand that the DNA stool test requires FDA approval and any coverage is contingent on that approval. ASC CAN proposes that Medicare re-evaluate the evidence if the test is recommended by widely accepted guidelines and approved by the FDA."

Response: CMS **a**ppreciates the support for the decision. We further note that the American Cancer Society released its updated colorectal cancer screening guidelines on March 5, 2008 and we have included the relevant portion of those guidelines above.

Comment: America's Health Insurance Plans (AHIP) submitted a comment that "concurs with CMS's proposed decision to not expand the colorectal cancer screening benefit to include coverage of the Screening DNA Stool Test." Specifically, the commenter stated that their "Health plans consider both premarket review and approval by the FDA as minimum pre-requisites for consideration of coverage. Given the FDA has determined that the only commercially available screening DNA stool test, PreGen-Plus™, requires premarket review, our community believes that coverage of this test is premature."

Response: We appreciate the supportive comment.

Comment: The United Health Group (UHG) agrees with the proposed decision to not expand the colorectal cancer screening benefit to include stool DNA tests, but believes the proposed decision should extend to both average-risk and persons at high-risk for colorectal cancer. They base their conclusion "not on the level of FDA review and approval, but the quality of clinical evidence supporting the use of stool DNA testing for colorectal cancer screening." Specifically, UHG notes that, "While current published clinical studies indicate that stool DNA testing can detect precancerous and cancerous lesions with moderate-to-high accuracy, there is insufficient evidence to conclude that stool DNA testing improves patient management or decreases mortality from colon cancer."

Response: We appreciate the support for the proposed decision to not expand the colorectal cancer screening benefit to include coverage of stool DNA tests for average- risk individuals. The issue of expanding the colorectal cancer screening benefit to include coverage of stool DNA tests for high-risk individuals, however, falls outside the scope of this NCD because the requester did not ask for coverage of this particular use of the test. We would note, however, that the present colorectal cancer screening benefit does not include coverage of the screening stool DNA test for either average-risk or high-risk individuals.

Comment: Two commenters offered conflicting information on whether a particular randomized multicenter trial to determine the efficacy and feasibility of stool DNA screening for colorectal cancer funded by the National Cancer Institute (NCI) is currently being conducted or not. One commenter suggested that a CMS decision on the medically necessary and appropriate use of stool DNA testing should await the results of this trial and the other believes that the study in question was completed four years ago.

Response: The issue as to whether a particular randomized multicenter trial to determine the efficacy and feasibility of stool DNA screening for colorectal cancer funded by NCI is currently being conducted falls outside the scope of this NCD. In future reconsiderations of this topic, additional evidence may be needed to demonstrate the adequacy of the stool DNA test for colorectal cancer screening in a multi-year interval.

Physicians

Comment: One physician stated he would not recommend the DNA stool test as an alternative to a colonoscopy to his patients because studies of the test show that its sensitivity to colorectal cancer is not sufficiently close to that of a colonoscopy and its use would likely result in a large number of false negatives (12% and 17%.) The commenter believes that “This should be unacceptable because these patients will falsely assume that they are cancer free and should not need another test for 5 years as recommended by the manufacturer.”

Response: We appreciate the support for the proposed decision not to expand the colorectal cancer screening benefit to include coverage of this test. Since there is no FDA cleared or approved, commercially available stool DNA test for colorectal cancer screening at this time, we proposed not to expand the colorectal cancer screening benefit to include coverage of this test.

General Public

Comment: Four commenters expressed disappointment with the proposed CMS decision not to expand the colorectal cancer screening benefit to include coverage of the screening DNA stool test. One commenter indicated that for the agency “To decline to cover this simple, cost effective, and non-invasive test because it lacks official FDA approval is an absurd and purely political decision that borders on criminal negligence.” A second stated that she believed that this type of test “is not only convenient but will help to save thousands of lives.” A third noted that “We need a test that can catch early stage cancers in the distal part of the colon, for which people can take a test in the privacy of their own home, with dignity.” A fourth commenter stated that the new test “would save taxpayers many millions of dollars by catching cancer while it is still curable…”

Response: Since there is no FDA cleared or approved, commercially available stool DNA test for colorectal cancer screening at this time, CMS will not expand the colorectal cancer screening benefit.

VII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage.

For purposes of this scope of benefit NCD, the underlying authority for the colorectal cancer screening benefit is under § 1861(pp)(1)(D). Under our final rules effective March 1, 2003, the Secretary has modified the scope of the benefit to include "other tests or procedures established by a national coverage determination, and modifications to tests under this paragraph, with such frequency and payment limits as CMS determines appropriate, in consultation with appropriate organizations," as provided in 42 CFR 410.37(a)(1)(v). 67 Fed. Reg. 79966, 80040 (December 31, 2002). In view of the request from Exact Sciences for coverage of their test every 5 years as an alternative to a screening colonoscopy that may be covered every 10 years or as an alternative to a screening flexible sigmoidoscopy that may be covered every 4 years for average risk individuals, we are using the national coverage determination authority under 42 CFR 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include the DNA stool test.

During our analysis of this test, an unexpected event occurred that profoundly affects market availability of the technology. In October 2007, the FDA stated that the PreGen-Plus™ test is a medical device that requires FDA clearance or approval prior to marketing (Appendix A). In December 2007, CMS received a letter from Exact Sciences describing the current situation and requesting a withdrawal of their initial request. This lack of availability of the test profoundly affects our assessment of it. In the absence of an FDA determination, CMS believes that there may be unresolved questions regarding the safety and effectiveness of the stool DNA test.

Since there is no FDA cleared or approved, commercially available stool DNA test for CRC screening at this time, CMS does not believe that identification of stool DNA mutations is an appropriate CRC screening test. Therefore, CMS proposes not to expand the colorectal cancer screening benefit to include coverage of this test. After a commercially available stool DNA test is cleared or approved by the FDA, a request for reconsideration would be anticipated.

VII.Decision

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS will not expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

Appendix A: FDA Letter to Exact Sciences (PDF, 85KB)

---

[1] The coverage of screening colonoscopy was expanded by the Benefits Improvements and Protection Act of 2000 to include beneficiaries at average risk every 10 years, effective January 1, 2002. Public Law No. 106-554, § 103 (2000).

[2] Individuals at high risk for colorectal cancer means an individual with (1) a close relative who has had colorectal cancer or adenomatous polyp; (2) family history of familial adenomatous polyposis; (3) family history of hereditary nonpolyposis colorectal cancer, (4) personal history of adenomatous polyps; (5) personal history of colorectal cancer; or (6) inflammatory bowel disease, including Crohn's disease and ulcerative colitis. See § 1861(pp)(2) of the Social Security Act.

Back to Top

Bibliography

Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroentereology 2000;119:1219-1227.

Blue Cross Blue Shield Technology Evaluation Center. Fecal DNA special report: Analysis for colon cancer screening. BCBS TEC Assessment Program 2006; Volume 21, No. 6 (at http://www.bcbs.com/blueresources/tec/vols/21/21_06.pdf).

Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. New England Journal of Medicine 2004;351:2704-14.

Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Published online at: http://caonline.amcancersoc.org/cgi/content/full/CA.2007.0018v1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&titleabstract=guidelines&searchid=1074190906250_391&stored_search=&FIRSTINDEX=0&journalcode=canjclin (accessed March 17, 2008).

Syngal S, Stoffel E, Chung D, et al. Detection of stool DNA mutations before and after treatment of colorectal neoplasia. Cancer 2006;106:277-283.

Tagore KS, Lawson MJ, Yucaitis JA, et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. Clinical Colorectal Cancer 2003;3:47-43.

U.S. Preventive Services Task Force. Screening for colorectal cancer: recommendations and rationale. Agency for Healthcare Research and Quality 2002 (at http://www.ahrq.gov/clinic/3rduspstf/colorectal/colorr.htm).

Winawer S, Fletcher R, Rex D,et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology. 2003 Feb;124(2):544-60.

Zauber AG, Lansdorp-Vogelaar I, Wilschut J, et al. Cost-effectiveness of DNA stool testing to screen for colorectal cancer. AHRQ Technology Assessment Program 2007 (at http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=212).

Back to Top